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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/718,355	11/24/2000	Guy A. Rouleau	10112102/GOUD:023US	3085

32425 7590 04/16/2007

FULBRIGHT & JAWORSKI L.L.P.
600 CONGRESS AVE.
SUITE 2400
AUSTIN, TX 78701

EXAMINER	
KOLKER, DANIEL E	
ART UNIT	**PAPER NUMBER**
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

A

Office Action Summary	Application No.	Applicant(s)	
	09/718,355	ROULEAU ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/11/06, 1/29/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Seq alignment*.

DETAILED ACTION

1. The remarks, amendments, and declaration filed 29 January 2007 have been entered. Claims 1 – 41 are canceled; claims 42 – 57 are new.

2. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649.

Continued Examination Under 37 CFR 1.114

3. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 29 January 2007 has been entered.

Withdrawn Rejections and Objections

4. Any rejection of record not reiterated herein is withdrawn. With respect to the rejection under 35 USC 112, first paragraph, for lack of enablement commensurate in scope with the claims, applicant presented arguments and a declaration filed under 37 CFR 1.132 to support the assertion that the specification is enabling for methods of selecting compounds which reduce the activity of a sodium channel, wherein the channel is a variant at least 95% identical to a protein encoded by SEQ ID NO:1 or 2. The declaration under 37 CFR 1.132 filed 29 January 2007 is sufficient to overcome the rejection based upon lack of enablement commensurate in scope with the claims. The examiner concedes that the degree of experimentation required in order to practice the full scope of the claimed methods is not undue, and notes that while there is not an explicit recitation of function for the variant proteins (i.e. those encompassed by claim 42, part iii), the methods necessarily require sodium channels which have sodium channel activity; see for example claim 42 parts (b) and (c). Further, the activity of sodium channels was well-known in the prior art, as indicated by applicant's citation of several prior art publications (declaration, page 3, final paragraph).

Information Disclosure Statement

5. The information disclosure statement filed 11 October 2006 has been considered. Reference C10 has been crossed off. Applicant has not submitted the complete sequences of the referenced GenBank sequence. What has been submitted is a partial printout of an

alignment between AF035685 and SEQ ID NO:65 from 10/664422. However note that the entire alignment is not enclosed; the end of page 2 indicates that certain bases appear on the next page.

The information disclosure statement filed 29 January 2007 has been considered. Entry C15 has been amended by the examiner to indicate that only a single page has been received, as opposed to 774 pages as written by applicant. The examiner is unable to determine the contents of the book referred to in the citation as it has not been submitted. Should applicant desire particular articles or chapters from the book to be considered by the examiner, applicant may of course submit them.

Entry C17, entitled "BLAST result" has been crossed off the IDS. A single sheet was submitted indicating that two sequences were compared and that no significant similarity was found. A handwritten note on the page is difficult to read. It is unclear whether the sequences compared were SEQ ID NO:12 and 13, or whether they were SEQ ID NO:72 and 73. Furthermore, the submitted document does not indicate the actual sequences that were submitted to the BLAST website, nor does it indicate when those sequences were published. The examiner is thus unable to determine what comparison was performed. Finally, as neither SEQ ID NO:12, 13, 72, or 73 is being claimed herein, it is not immediately obvious how the comparison is germane to patentability or examination. Should applicant desire particular accession numbers of particular databases be considered by the examiner, applicant may of course submit them.

Claim Objections

6. Claim 45 is objected to because of the following informalities: it is grammatically incorrect as it recites "...compound is library..."; the phrase appears to be missing an article such as "a". Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 45, 50 – 52, and 57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 45 is ambiguous because it is unclear how "said test compound", which clearly refers to a single test compound as recited in claim 42 part (a), can also be a library of many compounds. It is unclear whether one compound is in fact a library of compounds, or whether many compounds are to be considered to be a single compound.

Claim 50 is ambiguous because it is unclear what "induction of a second cellular messenger" actually refers to. It is not clear whether the phrase means that particular intracellular second messenger systems (for example, perhaps IP3 or cAMP) are induced, or alternatively whether several messengers are induced. By reciting "induction of a second cellular messenger" the claim implies that a first messenger is induced as well, but it is unclear what the first messenger is.

The scope of claim 51 is unclear because it depends from itself. Additionally, claim 51 recites the limitation "said flux of ions" in line 2. There is insufficient antecedent basis for this limitation in the claim. Claim 52 also depends from claim 51 and is unclear for the same reasons. Further claim 52 recites the limitation "said binding of molecules" in line 1. There is insufficient antecedent basis for this limitation in the claim. It appears that the rejection of claims 51 – 52 could be overcome if the claims were amended to depend from claim 50, rather than from claim 51. For the purposes of applying prior art, the examiner has presumed that claims 51 – 52 actually depend from claim 50.

The scope of claim 57 is unclear, because the recitation of a particular amino acid number (here 188), in the absence of a reference sequence, is ambiguous. This is particularly ambiguous given that the parent claim allows for variant proteins, which can differ by as much as 5% from a disclosed sequence and therefore can have several amino acids deleted, thereby altering the numbering scheme. It is unclear which amino acid residue is number 188.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 42 – 47, 49 – 51, 53 – 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Rechkziegel (1998. Journal of Physiology 509(Pt. 1):139-150, published May 1998).

Rechkziegel teaches contacting tissue from adult humans, which comprises central nervous system neurons, with candidate compounds. Rechkziegel is silent as to what the sequence of the sodium channels actually is, but the instant specification discloses that SEQ ID NO:3 is the protein sequence of adult SCN1A (sodium channel 1-alpha). Thus it is reasonable that the tissue samples from Rechkziegel comprise the protein of SEQ ID NO:3 as recited in claim 42 part (i), since the sodium channel 1-alpha protein is the main component of the channel (specification, p. 3). Note that claim 42 does not require recombinant expression of the channel, and thus encompasses channels residing in tissue samples. Rechkziegel further teaches contacting tissue with candidate compounds including tetrodotoxin (TTX) and saxitoxin (STX), measuring the activity of the sodium channel, and repeating the measurements in the absence of the test compounds. See Rechkziegel, Figure 3 as well as accompanying text on p. 144 ("Effects of TTX and STX"). Finally, Rechkziegel identifies TTX and STX as compounds which inhibit sodium channel activity, as the compounds bind to the sodium channel and prevent its opening. The reference therefore teaches every step of the method of claim 42 and includes the appropriate protein.

Claims 43 – 44 and 53 are rejected as they differ from claim 42 only in the intended use of the method, which is not given patentable weight; claims 43 – 44 and 53 require no additional steps or materials beyond what is recited in claim 42. Claim 45 is rejected as the two compounds TTX and STX are reasonably a "library", which need only include more than one compound. Claims 46 – 47 are rejected as they are product-by-process limitations. Note that they do not require any additional active steps, but rather refer to ways in which the proteins, which are starting materials in the claimed methods, are to be made. The protein starting material is the same no matter how it is made. Claim 49 is rejected as the channels are comprised in cells. Claims 50 – 51 are rejected as patch-clamp techniques were used to measure flux of ions through the channels (see p. 141 first paragraph). Claim 54 is rejected as it recites only a product-by-process limitation as to how the protein is made, furthermore all proteins within cells are made from nucleic acids which encode them. As SEQ ID NO:189 – 192 are all part of the SCN1A channel, the reference fairly anticipates claim 56 as well. The USPTO does not have the resources or ability to determine nucleic acid sequences. Should applicant

argue that the prior art method does not use a protein encoded by a nucleic acid which comprises at least one of SEQ IDNO:189 – 192, applicant should provide evidence that proteins encoded by these nucleic acids are patentably distinct from the prior art proteins. Once the PTO makes a prima facie case of inherency, the burdens shifts to applicant to distinguish the claimed invention from the prior art when the prior art is silent with respect to certain features which appear to be inherent; see MPEP § 2112, particularly subsections III and V.

9. Claims 42 – 47, 49, 50, and 53 are rejected under 35 U.S.C. 102(b) as being anticpated by Tian et al. (1995. Brain Research 680:164-172).

Tian teaches contacting tissue from rats, which comprises central nervous system neurons, with candidate compounds. The reference is silent with respect to the sequences of proteins contained therein, but the instant specification discloses that rat SCN1A channels are 95% identical to human channels (p. 7 lines 2 – 4) and are suitable for all aspects of the invention. As the tissue sample from Tian has sodium channels, and the specification admits that the rat sodium channels are suitable for the practice of the invention and are 95% identical to human channels (i.e. SEQ ID NO:3 and 4), the methods of Tian are on point to claim 42, particularly part (iii). Tian teaches contacting the composition (i.e. tissue) comprising the relevant channels with test compounds including TTX, measuring the activity (bursting activity, which is repetitive action potential firing), washing out the TTX, and repeating the measurements. See p. 169, Figure 6. Tian identifies TTX as a compound which inhibits sodium channel activity. The reference therefore teaches every step of the method of claim 42 and includes the appropriate protein.

Claims 43 – 44 and 53 are rejected as they differ from claim 42 only in the intended use of the method, which is not given patentable weight; claims 43 – 44 and 53 require no additional steps or materials beyond what is recited in claim 42. Claim 45 is rejected as the reference by Tian teaches several other compounds which are contacted with the composition; together these compounds reasonably constitute a "library". Claims 46 – 47 are rejected as they are product-by-process limitations. Note that they do not require any additional active steps, but rather refer to ways in which the proteins, which are starting materials in the claimed methods, are to be made. The protein starting material is the same no matter how it is made. Claim 49 is rejected as the channels are comprised in cells. Claim 50 is rejected as Figure 6 shows a change in current, as measured in nanoamperes.

10. Claims 42 – 47, 49 – 50, and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Noda et al. (1987). Journal of Receptor Research 7(1-4):467-497.

Noda teaches rat sodium channels which are 2009 amino acids long and are 98.5% identical to applicant's SEQ ID NO:4 (see enclosed alignment, see also Noda p. 469 final paragraph and Figure 2). The proteins are thus within the scope of claim 42, particularly part iii, as the proteins are encoded by nucleic acids (see Noda, Figure 2), and the specification discloses that SEQ ID NO:2 encodes SEQ ID NO:4. Thus it is apparent that the protein from Noda is encoded by a sequence at least 95% identical to SEQ ID NO:2. Noda teaches contacting cells carrying the nucleic acids encoding this protein with agents; see p. 469 for identification of cells carrying the nucleic acids in vectors (and therefore on point to claims 46 – 47) as well as p. 485 which indicates that cells expressing the vectors were contacted with TTX. Note that Noda teaches the percentage of the current which is TTX-sensitive and therefore it is reasonable that the authors measured the amount of sodium channel activity in both the presence and absence of TTX. Noda teaches that TTX prevents sodium channel activity, and therefore is on point to element (d) of claim 42. Claims 43 – 44 and 53 are rejected as they differ from claim 42 only in the intended use of the method, which is not given patentable weight; claims 43 – 44 and 53 require no additional steps or materials beyond what is recited in claim 42. Claim 45 is rejected because it is apparent that applicant considers a single compound to be a library. Claim 49 is rejected as the cells used in the assay are whole cells (Xenopus oocytes). Claim 50 is rejected as the reference by Noda reports that changes in currents are measured.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 42 – 51, and 53 – 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rechkziegel (1998. Journal of Physiology 509(Pt. 1):139-150, published May 1998) in view of Hartshorne (1984. Journal of Biological Chemistry 259:1667 – 1675).

The reasons why claims 42 – 47, 49 – 51, and 53 – 54 are anticipated by Rechkziegel are set forth above. The reference teaches screening sodium channels for antagonists which bind to the channels including STX and TTX, but does not teach cell-free assays as recited in claim 48.

Hartshorne teaches purifying sodium channels to homogeneity from tissue and teaches that the purified channels are able to bind STX. The reference teaches that the isolation process increases the concentration of sodium channels over 1300-fold. However Hartshorne does not explicitly teach screening methods as recited in claim 42.

It would have been obvious to one of ordinary skill in the art to use the cell-free binding assays described by Hartshorne in the screening assays of Rechkziegel, with a reasonable expectation of success. The artisan of ordinary skill would be motivated to use the purified channels and cell-free binding assay, because doing so would allow the artisan to use considerably less of the agents to be screened, thereby reducing costs. Furthermore, the artisan of ordinary skill would be motivated to use in vitro binding assays as both references teach that those agents which bind to the STX binding site block the channel activity, thus screening for binding to this region would identify sodium channel blockers. The in vitro cell-free binding assay would be advantageous, because it can easily be scaled up to allow for screening of many agents, whereas the scaling up an in vivo assay such as that described by Rechkziegel would be difficult and expensive, given the high cost of electrophysiological recording equipment. This would be immediately obvious to the artisan upon reading the references, as the Hartshorne reference teaches that STX-binding activity is retained, and the substantial increase in purity would mean that much less of a candidate compound would be needed in a given reaction volume.

12. Claims 42 – 47 and 49 – 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rechkziegel (1998. Journal of Physiology 509(Pt. 1):139-150, published May 1998) in view of Kienle (1997. Biosensors and Bioelectronics 12:779-786).

The reasons why claims 42 – 47, 49 – 51, and 53 – 54 are anticipated by Rechkziegel are set forth above. The reference teaches screening sodium channels for antagonists including STX and TTX, but does not teach using surface plasmon resonance, as recited in claim 52, to detect the interaction between the putative antagonists and the channel.

Kienle teaches use of surface plasmon resonance, as recited in claim 52, to identify agents which bind to rat cardiac sodium channels, which are functionally similar to the sodium channels in claim 42. The reference by Kienle teaches that surface plasmon resonance is a powerful tool that offers many advantages in identifying interactions between a ligand (for example, an antagonist) and a receptor (i.e. a channel). These advantages are listed on p. 779 second column and include that the technique allows for label-free detection, and that it is direct and non-invasive. Further the technique allows for measurement of kinetic rate constants and affinity constants, both of which are useful for the artisan to know when developing drugs. However, Kienle does not teach screening assays using the specific sodium channels recited in claim 42.

It would have been obvious to one of ordinary skill in the art to modify the assays of Rechkziegel, which screen for antagonists that bind to sodium channels, to include the surface plasmon resonance technique taught by Kienle, with a reasonable expectation of success. The motivation to modify the assays would be to take advantage of the addition information provided by the surface plasmon resonance technique, including kinetic rate and affinity constants.

13. Claims 42 – 47, 49 – 51, and 53 – 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rechkziegel (1998. Journal of Physiology 509(Pt. 1):139-150, published May 1998) in view of Avanzini (1996. Progressive Nature of Epileptogenesis (Epilepsy Res. Suppl. 12), pp. 53 – 61).

The reasons why claims 42 – 47, 49 – 51, and 53 – 54 are anticipated Rechkziegel are set forth above. Briefly, the reference teaches contacting brain tissue from adult humans, which comprises the protein of SEQ ID NO:3, with candidate agents and determining whether the agents reduce sodium channel activity as recited in claim 42. Rechkziegel teaches compositions which comprise SEQ ID NO:3, as recited in claims 42 and 54, but does not teach

compositions comprising the juvenile form of the sodium channel, i.e. that "obtained from a nucleic acid encoding SEQ ID NO:4" as recited in claim 55.

Avanzini teaches that there are several forms of epilepsy which are unique to human infants and which have onset at very early age (<1 yr., see Avanzini p. 53 first column). Avanzini teaches that there has been difficulty in reproducing the features of these early infantile forms of epilepsy in animal models, thereby indicating to the artisan of ordinary skill that there is a need to screen for agents which could treat epilepsy in humans. Avanzini teaches performing experiments with neural tissue from juvenile rats (see Methods section), and teaches that in juvenile tissue inhibitory post-synaptic potentials are not present (p. 53 second column), indicating neurons are likely to be hyper-excitable. Avanzini teaches contacting tissue comprising juvenile rat sodium channels with TTX (p. 54 second column). However Avanzini does not teach performing screening assays to find drugs which reduce sodium channel activity in tissue from juvenile humans.

It would have been obvious to one of ordinary skill in the art to modify the experiments of Rechkziegel to use neonatal human tissue rather than adult human tissue, as suggested by Avanzini, thereby arriving at the screening assay wherein a composition comprising SEQ ID NO:4, the neonatal form of the SCN1A channel, is present and therefore on point to claim 55. The motivation to do so would be to find agents which inhibit the activity of the neonatal sodium channels; this motivation comes directly from the from the Avanzini reference which points out that neonatal epilepsies are qualitatively different from those seen in adults and discusses the limits of animal models for these forms of epilepsy. Thus the artisan of ordinary skill would be motivated to use tissue from neonatal humans in the screening assays in order to overcome these limitations.

Conclusion

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Daniel E. Kolker, Ph.D.
April 10, 2007

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER

Applicant's SEQ ID NO:4 aligned w/ Noda et al. (2009 amino acid seq).

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<!--StartFragment-->RESULT 3
SCN1A_RAT
ID   SCN1A_RAT      STANDARD;      PRT;  2009 AA.
AC   P04774;
DT   13-AUG-1987, integrated into UniProtKB/Swiss-Prot.
DT   13-AUG-1987, sequence version 1.
DT   27-JUN-2006, entry version 67.
DE   Sodium channel protein type 1 subunit alpha (Sodium channel protein
DE   type I subunit alpha) (Voltage-gated sodium channel subunit alpha
DE   Nav1.1) (Sodium channel protein, brain I subunit alpha).
GN   Name=Scn1a;
OS   Rattus norvegicus (Rat).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Euarchontoglires; Glires; Rodentia; Sciurognathi;
OC   Muroidea; Muridae; Murinae; Rattus.
OX   NCBI_TaxID=10116;
RN   [1]
RP   NUCLEOTIDE SEQUENCE [MRNA].
RX   MEDLINE=86146901; PubMed=3754035; DOI=10.1038/320188a0;
RA   Noda M., Ikeda T., Kayano T., Suzuki H., Takeshima H., Kurasaki M.,
RA   Takahashi H., Numa S.;
RT   "Existence of distinct sodium channel messenger RNAs in rat brain.";
RL   Nature 320:188-192(1986).
RN   [2]
RP   NUCLEOTIDE SEQUENCE [MRNA].
RX   MEDLINE=87311395; PubMed=2442385;
RA   Noda M., Numa S.;
RT   "Structure and function of sodium channel.";
RL   J. Recept. Res. 7:467-497(1987).
RN   [3]
RP   NUCLEOTIDE SEQUENCE [MRNA] OF 177-253.
RC   STRAIN=Sprague-Dawley; TISSUE=Brain;
RX   MEDLINE=92051314; PubMed=1658739;
RA   Sarao R., Gupta S.K., Auld V.J., Dunn R.J.;
RT   "Developmentally regulated alternative RNA splicing of rat brain
RT   sodium channel mRNAs.";
RL   Nucleic Acids Res. 19:5673-5679(1991).
CC   -!- FUNCTION: Mediates the voltage-dependent sodium ion permeability
CC       of excitable membranes. Assuming opened or closed conformations in
CC       response to the voltage difference across the membrane, the
CC       protein forms a sodium-selective channel through which Na(+) ions
CC       may pass in accordance with their electrochemical gradient.
CC   -!- SUBUNIT: The sodium channel consists of a large polypeptide and 2-
CC       3 smaller ones. This sequence represents a large polypeptide.
CC   -!- SUBCELLULAR LOCATION: Membrane; multi-pass membrane protein.
CC   -!- DOMAIN: The sequence contains 4 internal repeats, each with 5
CC       hydrophobic segments (S1,S2,S3,S5,S6) and one positively charged
CC       segment (S4). Segments S4 are probably the voltage-sensors and are
CC       characterized by a series of positively charged amino acids at
CC       every third position.
CC   -!- SIMILARITY: Belongs to the sodium channel family.
CC   -!- SIMILARITY: Contains 1 IQ domain.
CC   ---------------------------------------------------------------------
CC   Copyrighted by the UniProt Consortium, see http://www.uniprot.org/terms
CC   Distributed under the Creative Commons Attribution-NoDerivs License
CC   ---------------------------------------------------------------------
DR   EMBL; X03638; CAA27286.1; -; mRNA.
DR   EMBL; M22253; AAA79965.1; -; mRNA.
DR   PIR; A25019; A25019.
DR   UniGene; Rn.32079; -.
DR   HSSP; P04775; 1BYY.
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DR   RGD; 69364; Scn1a.
DR   GO; GO:0005248; F:voltage-gated sodium channel activity; TAS.
DR   GO; GO:0019228; P:generation of action potential; TAS.
DR   InterPro; IPR001682; Ca/Na_pore.
DR   InterPro; IPR002111; Cat_channel_TrpL.
DR   InterPro; IPR011992; EF-Hand_type.
DR   InterPro; IPR005821; Ion_trans.
DR   InterPro; IPR000048; IQ_CaM_bd_region.
DR   InterPro; IPR005820; M+channel_nlg.
DR   InterPro; IPR001696; Na_channel.
DR   InterPro; IPR008051; Na_channel1.
DR   InterPro; IPR010526; Na_trans_assoc.
DR   Pfam; PF00520; Ion_trans; 4.
DR   Pfam; PF00612; IQ; 1.
DR   Pfam; PF06512; Na_trans_assoc; 1.
DR   PRINTS; PR00170; NACHANNEL.
DR   PRINTS; PR01664; NACHANNEL1.
DR   PROSITE; PS50096; IQ; FALSE_NEG.
KW   Glycoprotein; Ion transport; Ionic channel; Membrane; Repeat; Sodium;
KW   Sodium channel; Sodium transport; Transmembrane; Transport;
KW   Voltage-gated channel.
FT   CHAIN         1   2009       Sodium channel protein type 1 subunit
FT                                alpha.
FT                                /FTId=PRO_0000048490.
FT   TRANSMEM    124    147       S1 of repeat I.
FT   TRANSMEM    156    175       S2 of repeat I.
FT   TRANSMEM    189    207       S3 of repeat I.
FT   TRANSMEM    214    233       S4 of repeat I.
FT   TRANSMEM    250    273       S5 of repeat I.
FT   TRANSMEM    400    425       S6 of repeat I.
FT   TRANSMEM    763    787       S1 of repeat II.
FT   TRANSMEM    799    822       S2 of repeat II.
FT   TRANSMEM    831    850       S3 of repeat II.
FT   TRANSMEM    857    876       S4 of repeat II.
FT   TRANSMEM    893    913       S5 of repeat II.
FT   TRANSMEM    967    992       S6 of repeat II.
FT   TRANSMEM   1214   1237       S1 of repeat III.
FT   TRANSMEM   1251   1276       S2 of repeat III.
FT   TRANSMEM   1283   1304       S3 of repeat III.
FT   TRANSMEM   1309   1330       S4 of repeat III.
FT   TRANSMEM   1350   1377       S5 of repeat III.
FT   TRANSMEM   1457   1483       S6 of repeat III.
FT   TRANSMEM   1537   1560       S1 of repeat IV.
FT   TRANSMEM   1572   1595       S2 of repeat IV.
FT   TRANSMEM   1602   1625       S3 of repeat IV.
FT   TRANSMEM   1636   1657       S4 of repeat IV.
FT   TRANSMEM   1673   1695       S5 of repeat IV.
FT   TRANSMEM   1762   1786       S6 of repeat IV.
FT   REPEAT      110    454       I.
FT   REPEAT      750   1022       II.
FT   REPEAT     1200   1514       III.
FT   REPEAT     1523   1821       IV.
FT   CARBOHYD    211    211       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    284    284       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    295    295       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    301    301       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    306    306       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    338    338       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    601    601       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    621    621       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD    681    681       N-linked (GlcNAc. . .) (Potential).
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FT   CARBOHYD    892    892       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD   1060   1060       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD   1064   1064       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD   1080   1080       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD   1146   1146       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD   1378   1378       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD   1392   1392       N-linked (GlcNAc. . .) (Potential).
FT   CARBOHYD   1403   1403       N-linked (GlcNAc. . .) (Potential).
SQ   SEQUENCE   2009 AA;  228770 MW;  6808466F6368373B CRC64;

  Query Match             98.5%;  Score 10244;  DB 1;  Length 2009;
  Best Local Similarity   98.0%;  Pred. No. 0;
  Matches 1969;  Conservative   26;  Mismatches   14;  Indels    0;  Gaps    0;

Qy          1 MEQTVLVPPGPDSFNFFTRESLAAIERRIAEEKAKNPKPDKKDDDENGPKPNSDLEAGKN 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MEQTVLVPPGPDSFNFFTRESLAAIERRIAEEKAKNPKPDKKDDDENGPKPNSDLEAGKN 60

Qy         61 LPFIYGDIPPEMVSEPLEDLDPYYINKKTFIVLNKGKAIFRFSATSALYILTPFNPLRKI 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 LPFIYGDIPPEMVSEPLEDLDPYYINKKTFIVLNKGKAIFRFSATSALYILTPFNPLRKI 120

Qy        121 AIKILVHSLFSMLIMCTILTNCVFMTMSNPPDWTKNVEYTFTGIYTFESLIKIIARGFCL 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 AIKILVHSLFSMLIMCTILTNCVFMTMSNPPDWTKNVEYTFTGIYTFESLIKIIARGFCL 180

Qy        181 EDFTFLRDPWNWLDFTVITFAFVTEFVNLGNFSALRTFRVLRALKTISVIPGLKTIVGAL 240
              ||||||||||||||||||||:|||||:||| ||||||||||||||||||||||||||||
Db        181 EDFTFLRDPWNWLDFTVITFAYVTEFVDLGNVSALRTFRVLRALKTISVIPGLKTIVGAL 240

Qy        241 IQSVKKLSDVMILTVFCLSVFALIGLQLFMGNLRNKCIQWPPTNASLEEHSIEKNITVNY 300
              ||||||||||||||||||||||||||||||||||:||||||||||||||||||:| :|
Db        241 IQSVKKLSDVMILTVFCLSVFALIGLQLFMGNLRNKCVQWPPTNASLEEHSIEKNVTTDY 300

Qy        301 NGTLINETVFEFDWKSYIQDSRYHYFLEGFLDALLCGNSSDAGQCPEGYMCVKAGRNPNY 360
              ||||:|||||||||||||||||||||| ||||||||||||||||||||||||||||||||
Db        301 NGTLVNETVFEFDWKSYIQDSRYHYFLEGVLDALLCGNSSDAGQCPEGYMCVKAGRNPNY 360

Qy        361 GYTSFDTFSWAFLSLFRLMTQDFWENLYQLTLRAAGKTYMIFFVLVIFLGSFYLINLILA 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 GYTSFDTFSWAFLSLFRLMTQDFWENLYQLTLRAAGKTYMIFFVLVIFLGSFYLINLILA 420

Qy        421 VVAMAYEEQNQATLEEAEQKEAEFQQMIEQLKKQQEAAQQAATATASEHSREPSAAGRLS 480
              ||||||||||||||||||||||||:|||||||||||||| ||||||||||||||||
Db        421 VVAMAYEEQNQATLEEAEQKEAEFQQMLEQLKKQQEAAQQAAAATASEHSREPSAAGRLS 480

Qy        481 DSSSEASKLSSKSAKERRNRRKKRKQKEQSGGEEKDEDEFQKSESEDSIRRKGFRFSIEG 540
              ||||||||||||||||||||||||||||||||||:||| ||||||||||||||||||
Db        481 DSSSEASKLSSKSAKERRNRRKKRKQKEQSGGEEKDDDEFHKSESEDSIRRKGFRFSIEG 540

Qy        541 NRLTYEKRYSSPHQSLLSIRGSLFSPRRNSRTSLFSFRGRAKDVGSENDFADDEHSTFED 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        541 NRLTYEKRYSSPHQSLLSIRGSLFSPRRNSRTSLFSFRGRAKDVGSENDFADDEHSTFED 600

Qy        601 NESRRDSLFVPRRHGERRNSNLSQTSRSSRMLAVFPANGKMHSTVDCNGVVSLVGGPSVP 660
              |||||||||||||||||||||||||||||  ||||||||||||||||||||||||
Db        601 NESRRDSLFVPRRHGERRNSNLSQTSRSSRMLAGLPANGKMHSTVDCNGVVSLVGGPSVP 660

Qy        661 TSPVGQLLPEVIIDKPATDDNGTTTETEMRKRRSSSFHVSMDFLEDPSQRQRAMSIASIL 720
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        661 TSPVGQLLPEVIIDKPATDDNGTTTETEMRKRRSSSFHVSMDFLEDPSQRQRAMSIASIL 720
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Qy        721 TNTVEELEESRQKCPPCWYKFSNIFLIWDCSPYWLKVKHVVNLVVMDPFVDLAITICIVL 780
              ||||||||||||||||||||||||||||||||||||||||:||||||||||||||||||||
Db        721 TNTVEELEESRQKCPPCWYKFSNIFLIWDCSPYWLKVKHIVNLVVMDPFVDLAITICIVL 780

Qy        781 NTLFMAMEHYPMTDHFNNVLTVGNLVFTGIFTAEMFLKIIAMDPYYYFQEGWNIFDGFIV 840
              |||||||||||||:|||:||||||||||||||||||||||||||||||||||||||||||
Db        781 NTLFMAMEHYPMTEHFNHVLTVGNLVFTGIFTAEMFLKIIAMDPYYYFQEGWNIFDGFIV 840

Qy        841 TLSLVELGLANVEGLSVLRSFRLLRVFKLAKSWPTLNMLIKIIGNSVGALGNLTLVLAII 900
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        841 TLSLVELGLANVEGLSVLRSFRLLRVFKLAKSWPTLNMLIKIIGNSVGALGNLTLVLAII 900

Qy        901 VFIFAVVGMQLFGKSYKDCVCKIASDCQLPRWHMNDFFHSFLIVFRVLCGEWIETMWDCM 960
              ||||||||||||||||||||||:||:||||||||||||||||||||||||||||||||||
Db        901 VFIFAVVGMQLFGKSYKDCVCKIATDCKLPRWHMNDFFHSFLIVFRVLCGEWIETMWDCM 960

Qy        961 EVAGQAMCLTVFMMVMVIGNLVVLNLFLALLLSSFSADNLAATDDDNEMNNLQIAVDRMH 1020
              |||||||||||||||| ||||||||||||||||||||||||||||||||||||||||||||
Db        961 EVAGQAMCLTVFMMVMVIRNLVVLNLFLALLLSSFSADNLAATDDDNEMNNLQIAVDRMH 1020

Qy       1021 KGVAYVKRKIYEFIQQSFIRKQKILDEIKPLDDLNNKKDSCMSNHTAEIGKDLDYLKDVN 1080
              ||||||||||||||||||:||||||||||||||||:||:| |||| ||||||| |||||
Db       1021 KGVAYVKRKIYEFIQQSFVRKQKILDEIKPLDDLNNRKDNCTSNHTTEIGKDLDCLKDVN 1080

Qy       1081 GTTSGIGTGSSVEKYIIDESDYMSFINNPSLTVTVPIAVGESDFENLNTEDFSSESDLEE 1140
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1081 GTTSGIGTGSSVEKYIIDESDYMSFINNPSLTVTVPIAVGESDFENLNTEDFSSESDLEE 1140

Qy       1141 SKEKLNESSSSSEGSTVDIGAPVEEQPVVEPEETLEPEACFTEGCVQRFKCCQINVEEGR 1200
              |||||||||||||||||||| ||||||:||||||||||||||||||||||:||||||
Db       1141 SKEKLNESSSSSEGSTVDIGAPAEEQPVMEPEETLEPEACFTEGCVQRFKCCQISVEEGR 1200

Qy       1201 GKQWWNLRRTCFRIVEHNWFETFIVFMILLSSGALAFEDIYIDQRKTIKTMLEYADKVFT 1260
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1201 GKQWWNLRRTCFRIVEHNWFETFIVFMILLSSGALAFEDIYIDQRKTIKTMLEYADKVFT 1260

Qy       1261 YIFILEMLLKWVAYGYQTYFTNAWCWLDFLIVDVSLVSLTANALGYSELGAIKSLRTLRA 1320
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1261 YIFILEMLLKWVAYGYQTYFTNAWCWLDFLIVDVSLVSLTANALGYSELGAIKSLRTLRA 1320

Qy       1321 LRPLRALSRFEGMRVVVNALLGAIPSIMNVLLVCLIFWLIFSIMGVNLFAGKFYHCINTT 1380
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||:|||
Db       1321 LRPLRALSRFEGMRVVVNALLGAIPSIMNVLLVCLIFWLIFSIMGVNLFAGKFYHCVNTT 1380

Qy       1381 TGDRFDIEDVNNHTDCLKLIERNETARWKNVKVNFDNVGFGYLSLLQVATFKGWMDIMYA 1440
              ||| |:| :||||:||||||||||||||||||||||||||||||||||||||||||||||
Db       1381 TGDTFEITEVNNHSDCLKLIERNETARWKNVKVNFDNVGFGYLSLLQVATFKGWMDIMYA 1440

Qy       1441 AVDSRNVELQPKYEESLYMYLYFVIFIIFGSFFTLNLFIGVIIDNFNQQKKKFGGQDIFM 1500
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1441 AVDSRNVELQPKYEESLYMYLYFVIFIIFGSFFTLNLFIGVIIDNFNQQKKKFGGQDIFM 1500

Qy       1501 TEEQKKYYNAMKKLGSKKPQKPIPRPGNKFQGMVFDFVTRQVFDISIMILICLNMVTMMV 1560
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1501 TEEQKKYYNAMKKLGSKKPQKPIPRPGNKFQGMVFDFVTRQVFDISIMILICLNMVTMMV 1560

Qy       1561 ETDDQSEYVTTILSRINLVFIVLFTGECVLKLISLRHYYFTIGWNIFDFVVVILSIVGMF 1620
              ||||||:|||:||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1561 ETDDQSDYVTSILSRINLVFIVLFTGECVLKLISLRHYYFTIGWNIFDFVVVILSIVGMF 1620
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Qy       1621 LAELIEKYFVSPTLFRVIRLARIGRILRLIKGAKGIRTLLFALMMSLPALFNIGLLLFLV 1680
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1621 LAELIEKYFVSPTLFRVIRLARIGRILRLIKGAKGIRTLLFALMMSLPALFNIGLLLFLV 1680

Qy       1681 MFIYAIFGMSNFAYVKREVGIDDMFNFETFGNSMICLFQITTSAGWDGLLAPILNSKPPD 1740
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1681 MFIYAIFGMSNFAYVKREVGIDDMFNFETFGNSMICLFQITTSAGWDGLLAPILNSKPPD 1740

Qy       1741 CDPNKVNPGSSVKGDCGNPSVGIFFFVSYIIISFLVVVNMYIAVILENFSVATEESAEPL 1800
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1741 CDPNKVNPGSSVKGDCGNPSVGIFFFVSYIIISFLVVVNMYIAVILENFSVATEESAEPL 1800

Qy       1801 SEDDFEMFYEVWEKFDPDATQFMEFEKLSQFAAALEPPLNLPQPNKLQLIAMDLPMVSGD 1860
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1801 SEDDFEMFYEVWEKFDPDATQFMEFEKLSQFAAALEPPLNLPQPNKLQLIAMDLPMVSGD 1860

Qy       1861 RIHCLDILFAFTKRVLGESGEMDALRIQMEERFMASNPSKVSYQPITTTLKRKQEEVSAV 1920
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1861 RIHCLDILFAFTKRVLGESGEMDALRIQMEERFMASNPSKVSYQPITTTLKRKQEEVSAV 1920

Qy       1921 IIQRAYRRHLLKRTVKQASFTYNKNKIKGGANLLIKEDMIIDRINENSITEKTDLTMSTA 1980
             ||||||||||||||||||||||||||:|||||||:||||||||||||||||||||||||||
Db       1921 IIQRAYRRHLLKRTVKQASFTYNKNKLKGGANLLVKEDMIIDRINENSITEKTDLTMSTA 1980

Qy       1981 ACPPSYDRVTKPIVEKHEQEGKDEKAKGK 2009
             |||||||||||||||||||||||||||||
Db       1981 ACPPSYDRVTKPIVEKHEQEGKDEKAKGK 2009
<!--EndFragment-->
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